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10/799,376	03/12/2004	Nina Finkelstein	1662/62005	7297

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,376	FINKELSTEIN ET AL.	
	Examiner	Art Unit	
	Patricia L. Morris	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-22,24-43 and 45-50* is/are pending in the application.

4a) Of the above claim(s) *6-12,19-22,24-40 and 46-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-18,41-43 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 13-18, 41-43 and 45 are under consideration in this application.

Claims 6-12, 19-22, 24-40 and 46-50 remain held withdrawn from consideration as being drawn to nonelected subject matter 37 CFR 1.142(b).

Election/Restrictions

The restriction requirement is deemed sound and proper and is hereby made FINAL.

Applicants' allegations regarding the interview summary record are noted, however, the record is deemed correct.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 13-18, 41-43 and 45 are rejected under 35 U.S.C. 102(a), (b) and/or (e) as being anticipated by Avrutov et al., Maimo and Kohl et al. I, II for the reasons set forth in the previous Office action.

Again, Avrutov et al., Maimo and Kohl et al. I, II specifically disclose the instant compound. Note claim 22 of Kohl et al. I, example 4 of Arrutov et al. or example 18 of Maimo. Hence, the instant compound is deemed anticipated therefrom.

Contra to applicants' arguments in the instant response, a novel chemical product is identified first by its "chemical nature", i.e., elemental and atom content. It is a well known fact that many pharmaceutical solids exhibit polymorphism which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice (see US Pharmacopia). Polymorphs are different crystalline forms of the **same pure substance** in which the molecules have different arrangements and/or different conformations of the molecules. Brittain concluded this per ponderous of conventional nature in the text book "Polymorphism in Pharmaceutical Solids" on page 2 that "*in the strictest sense, polymorphs are different crystalline forms of the* **same pure substance** *in which the molecules have different arrangements and/or different conformations of the molecules".*

Applicants merely cite a board decision and conclude the rejection is improper. Every application must be examined on its own merits. Further, applicants allege that the prior art compounds are not the same as the crystalline compounds since they fail to show the same powder X-ray diffraction patterns. However, applicants have failed to provide any objective evidence, *i.e.,* X-ray powder diffraction of a single cystal of the instant compounds *vis-à-vis* the prior art compounds at the same radiation parameters.

Applicants argue that the examiner has ignored the X-ray diffraction data. Applicants have failed to present any single X ray crystal diffraction of instant compound *vis-à-vis* the prior art compounds at the same parameters.

X-ray diffraction pattern **alone** does not demarcate the identity of two products. It is well recognized in the crystalline solid art that sometimes the difference in X-ray diffraction pattern is

very minor and must be carefully evaluated before a definitive conclusion is reached. See US Pharmacopia of record. Further, Davidovich et al. on page 16, states that changes in powder X-ray diffraction often resulted from experimental artifacts rather than polymorphism and that most of these changes were due to particle size/morphology, sample holder/preparation and instrument geometry. Note figure 4.21 on page 118 of Bernstein wherein the same compound shows two different X-ray patterns. Page 272 of Bernstein shows that two identical X-ray patterns, but one is the chemical compound pigment Yellow 14, wherein R is CH_3, while the other is the pigment Yellow 63, R is Cl. Thus, this is an example of identical X-ray displayed by different compounds. The figure on page 273 showed that two X-ray diffraction patterns collected on crystals and recrystals after melting. Although, there are new peaks, the authors concluded that "it may not be a pure medication", *i.e.,* not a true polymorph. Caira et al. recite several cases of "vanishing" polymorphs. Note page 165 therein.

The newly added references are supplied to as state-of-the-art evidence rebutting applicants' arguments in the instant response.

Claim Rejections - 35 USC ∋ 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13-18, 41-43 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Avrutov et al., Maimo and Kohl et al. I, II in view of Loqvist et al. (US 6,384,059), Finkelstein et al., Haleblian et al, Muzaffar et al., Chemical & Engineering News, US Pharmacopia., Jain et al, Taday et al., Brittain et al. and Concise Encyclopedia Chemistry for the reasons set forth in the previous Office action.

Again, Avrutov et al., Maimo and Kohl et al. I, II teach the crystal forms of the instant known compound and as well as the pharmaceutical compositions. Note example 4 of Avrutov et al. or claim 22 of Kohl. Loqvist et al. and Finkelstein et al. specifically teach that the instant compounds and analogous omeprazole are known to exist in additional crystalline forms. Haleblian et al., Muzaffar et al., Jain et al., Brittain et al. and Taday et al. teach that compounds exist as polymorphs. Chemical & Engineering News, Muzaffar et al., US Pharmacopia and Concise Encyclopedia teach that at any particular temperature and pressure, only one crystalline form is thermodynamically stable. Hence the claimed crystalline form as well as its relative selectivity of properties *vis-a-vis* the known compound are suggested by the references. It would appear obvious to one skilled in the art in view of the references that the instant compound would exist in different polymorphic forms. No unexpected or unobvious properties are noted.

Contra to applicants' assertions in the instant response, one having ordinary skill in the art would find the claims prima facie obvious because the instant claims differ from the known product merely by forms and the physical properties innate to the forms. It is well recognized in the pharmaceutical field that many solids exhibit polymorphism which is the innate nature of the particular drug. Note specifically Lovquist et al. and Finkelstein. Also, see US Pharmacopia. It also well recognized in the art that the different polymorphs will display different physical properties such as X-ray diffraction, melting point, etc. (see page 911 of Haleblian or page 33 of Chemical Engineering News). As clearly stated by Brittain (p.1-2) supra, as well as set forth by the court in In re Cofer 148 USPQ 268, ex parte Hartop 139 USPQ 525, that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom, are unpatentable. The instant claims are drawn to the ***same pure substance*** as the prior art that only have *different arrangements and/or different conformations of the molecule*. A mere difference in physical property is a well known conventional variation for the same pure substance is prima facie obvious. The instant compounds are not new as asserted by applicants.

Applicants merely provide unpublished Board decisions that reversed the examiner. The decisions are not persuasive because the allowance on one case has no bearing at all on another case. It is apparent that applicants need a reference to support that a **showing of unobvious properties is necessary.** Note Brittain et al., page 185 where it is stated: **"In 1990 Byrn and Pfeiffer found more than 350 patents on crystal forms granted on the basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, etc." Applicants have failed to show any advantage for the instant polymorphs.** Allegations by

applicants do not take the place of any objective evidence and continue to refuse to present any. It is well recognized in the art that the innately different polymorphs will display different physical properties such as X-ray diffraction pattern, melting point, etc. Just because it is "different" does not merit the new form patentable.

Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-43 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Again, there is a lack of description as to whether the pharmaceutical carriers are able to maintain the compound in the polymorphic form claimed. Processing a compound into a pharmaceutical composition could create a different polymorph than the polymorphs being claims or even back to the compound itself. See pages 912-913 of Habeblian. Jain et al., pages 322-326 teach that manufacturing processes affect polymorphs. Taday et al. on page 831, teach "..Once in the desired crystalline form, the polymorphic state may be changed by incorrect storage or even during tablet preparation". The specification fails to describe the pharmaceutical compositions claimed in terms of their X-ray diffraction pattern or infrared spectrum data. The

X-ray diffraction and Infrared spectrum data in the specification only pertains to the compounds rather than the compositions being claimed. Note Taday et al., page 836, figure 8, wherein the compound of four form in pharmaceutical composition resulted in similar spectra i.e. form.

Contra to applicants' arguments in the instant response, applicants have **failed to provide any objective evidence that the instant polymorphs are indeed maintained in the compositions.** Chemical & Engineering News discloses that formulation of drugs or pharmaceuticals in its metastable forms, for example, one polymorph, is highly unpredictable. The metastable forms will disappear and change into the most thermodynamically stable form. Muzaffar et al., page 60 states "At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form". And p. 63-65(a)-(h) pharmaceutical preparing processes affect polymorphism.

Contra to applicants' allegations, there is no description in the specification that the instant polymorphs keep their form in the pharmaceutical compositions. Applicants have failed to provide any objective evidence that the instant polymorphs are indeed maintained in the compositions. The preponderance of evidence in the state-of-the-art indicates that pharmaceutical compositions containing any particular crystalline form cannot be assumed. Also, note page 165 of Caira ,where it is specifically stated that polymorphs are known to "vanish" and attempts to regenerate the original polymorph are frequently met with failure.

Again, the specification lacks description of how the pharmaceutical composition can be prepared in order to maintain the particular compound of a particular form with the particular infrared spectra and X-ray diffraction being claimed. Disclosure of X-ray diffraction patterns for pharmaceutical compositions comprising the polymorphic forms are lacking in the specification.

The X-ray diffraction patterns and infrared spectra on pages 8-11 only supports the polymorphic forms of the compounds and not the pharmaceutical compositions. The specification has also not described how the polymorph forms and compositions being claimed will be maintained and prevented from converting to other forms when used in the treatment of diabetes mellitus and any and all unknown conditions associated therewith. Jain et al.., p 322-326, recite the manufacturing processes that affect polymorphs. Otsuka et al. On page 852 states « in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic phase transformation of the bulk CBZ powder during the manufacturing process".

Applicants' assertions and allegations in the instant response do not take the place of objective evidence. Applicants have failed to show that polymorph in the composition will maintain its form after pharmaceutical formulation. Applicants have provided no objective evidence that the instant polymorphs will not be identical to the prior art because *"when a crystalline solid is dissolved in solvent, the crystalline structure is lost so that different polymorphs of the same substance will show the same absorption spectra as solution"* (see Jain p.316). Further, in the aqueous phase, *all physical forms are amorphous* (see Ulicky). It is well recognized in the art that for a given crystalline form of a drug, *in absence of explicit* enabling description, in view of the high degree of unpredictability, even if one is in possession of a particular crystalline form, no predictability can be found in such form will prevail in pharmaceutical compositions. See Chemical & Engineering News.

Further, the specification has also not described how all the crystalline forms and compositions being claimed will be maintained and prevented from converting to other forms

when used in inhibiting gastric secretion. In addition, it is well recognized in the art that the compound is given to the subject in a physiological environment, i.e., administered. As discussed supra, there is no description or enabling support that the instant polymorph will be in its physical form and biological activity results from the particular form instead of the solution state of the compound.

The specification lacks direction or guidance for placing all of the alleged products in the possession of the public without inviting more than routine experimentation. Applicants are referred to In re Fouche, 169 USPQ 429 CCPA 1971, MPEP 716.02(b).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention

The nature of the invention is the preparation of polymorphic forms of the instant compoundt and compositions and for inhibiting gastric secretion.

State of the Prior Art

Polymorphs arise when molecules of a compound stack in the solid state in distinct ways. (See Chemical Engineering News, page 32). Although identical in chemical composition,

polymorphs can have very different properties. They are distinguishable by various analytical techniques, especially X-ray powder diffraction. Additionally, solids may form solvates. Polymorphs tend to convert from less stable to more stable forms. (See Chemical Engineering News, page 32). No method exists to predict the polymorphs of a solid compound with any significant certainty. In drug design, it is best work with the most stable polymorph, because it will not covert any further, however, the most stable polymorph usually is the least soluble. To improve bioavailability, drug companies sometimes trade off polymorph stability with solubility, choosing to work instead with the less stable forms first, also known as the metastable forms. Polymorphs can convert from one form to another during the manufacturing process of a pharmaceutical drug. See Chemical Engineering News. Page 33, which will changed the pharmacological affects of the drug. This is why it is important to monitor the polymorph during manufacture of the drug to see if it persists during manufacture.

The amount of direction or guidance and the presence or absence of working examples

Again, fFigures 1-4 of the specification only disclose the X-ray diffraction pattern and infrared spectra of compounds of particular forms rather than the compositions being claimed in terms of the specific X-ray diffraction patterns. Polymorphs often change into other polymorphs during drug manufacture (See Chemical Engineering News) into a pharmaceutical composition. Based on the unpredictability in the art, the applicant is not entitled to the X-ray diffraction patterns claimed for the pharmaceutical compositions.

Further, the specification fails to show that the instant polymorphs treat type II diabetes. As evidenced by the art of record, it is well known that polymorphs can convert to the original compound. Since only the thermodynamically stable form which can maintain its form after

formulation, the previous Office action stated that absent of such description of whether any metastable forms will spontaneously change into the thermodynamically forms or whether any metastable form will maintain its form after pharmaceutical formulation

The breadth of the claims

The breadth of the claims are drawn to the specific polymorph form and in addition to the pharmaceutical compositions and the method of inhibiting gastric secretion.

The quantity of experimentation needed

The quantity of experimentation needed would be undue when faced with the lack of direction and guidance present in the instant specification in regards to the pharmaceuticals compositions being claimed and verifying that they have the specific X-ray diffraction patterns being claimed which are not disclosed in the specification. There is also lack of guidance as to whether the instant polymorph rather than the original compound any gastric secretion.

In terms of the 8 Wands factors, undue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of unpredictability in the art of the invention, and the poor amount of direction provided by applicants. Taking the above factors into consideration, it is not seen where the instant claim is enabled by the instant application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-18, 41 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Again, claims 13-18, 41 and 45 contains the generic name pantoprazole. Where a generic name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the generic name cannot be used properly to identify any particular material or product. In the present case, the genreric name is used to identify/describe a chemical compound and, accordingly, the identification/description is indefinite. Again, the name pantoprazole does not properly identify the chemical structure of the compound.

Applicants merely assert that the name is a shorthand chemical name. This is not persuasive because only the chemical IUPAC name identifies the compound having a specific chemical structure.

Applicants merely cite patents that the term had been allowed. Applicants are invited to note that the claims along with the name **cite the chemical structure.**

The claims measure the invention. United Carbon Co. V. Binney & Smith Co., 55 USPQ 381 at 384, col. 1, end of 1st paragraph, Supreme Court of the United States (1942).

The U.S. Court of Claims held to this standard in Lockheed Aircraft Corp. v. United States, 193 USPQ 449, AClaims measure invention and resolution of invention must be based on what is claimed.

The C.C.P.A. in 1978 held that an invention is the subject matter defined by the claims submitted by the applicant. We have consistently held that no applicant should have limitations of the specification read into a claim where no express statement of the limitation is included in the claim. In re Priest, 199 USPQ 11, at 15.

Conclusion

No claim is allowed.

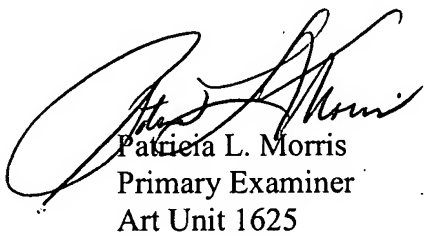
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia L. Morris whose telephone number is (571) 272-0688. The examiner can normally be reached on Mondays through Fridays.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Patricia L. Morris
Primary Examiner
Art Unit 1625

plm
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